

Previously, we speculated that a chronic inflammatory process or psychological distress during active disease could result in lower serum DHEA-S concentrations in patients with CIU.^{3–5} If so, it might be expected that DHEA-S concentration in blood would be raised upon long-term remission of urticaria. Indeed, in the present study, we observed some relationships between the clinical status (active disease or remission) and DHEA-S concentration. DHEA-S concentration was significantly lower in patients with symptomatic CIU as compared with those with CIU in remission, and as compared with healthy subjects. So far, it is unknown whether the decline in DHEA-S concentration precedes the onset of chronic urticaria, i.e. occurs before the first symptoms of the illness are observed, or appears later in consequence of a chronic illness. The lack of persistence of hormonal alterations, when the disease is clinically inactive, suggests that the mechanisms responsible for such change apply only throughout the active period of the disease and are most probably associated with distress.⁵ Undoubtedly, the symptoms of chronic urticaria, e.g. intense pruritus, give rise to distress.¹⁰ An unresolved question is whether restored serum DHEA-S concentration results in improved clinical status in urticaria or vice versa. Consequently, a further approach to determine DHEA-S behaviour in the course of urticaria would be a longitudinal study of patients with chronic recurrent urticaria. Such study would comprise multiple assessment of DHEA-S levels upon remission and during active disease as well as throughout the period directly preceding the urticaria symptoms; however, such a study would be difficult to perform and would take a long time.

Taken together, these data suggest that lower DHEA-S serum concentration is a transient and reversible phenomenon accompanying CIU, occurring during the active period and disappearing upon spontaneous remission of the disease. Explicit understanding of the changes in the hormonal environment may provide the basis to develop new therapeutic strategies.

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Caspase-1 activity of stratum corneum and serum interleukin-18 level are increased in patients with Netherton syndrome

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SIR, Netherton syndrome (NS) is an autosomal recessive inherited disorder characterized by congenital ichthyosis, trichorrhexis invaginata, and features of atopic dermatitis (AD) with high serum IgE levels.¹ The NS gene has been identified as SPINK5 (serine protease inhibitor Kazal-type 5) encoding the serine protease inhibitor LEKTI (lympho-epithelial Kazal-type related inhibitor).² Interleukin (IL)-18 induces immune responses associated with Th2 cells,³ and is synthesized as a pro-IL-18, which is activated by caspase-1.⁴ Caspase-1 is an intracellular cysteine protease produced as a procaspase-1 and activated by proteolytic cleavage.⁴ Caspase-1 and IL-18 may thus play critical roles in the development of AD. In this study, we determined serum IL-18 levels and caspase-1 activity in the stratum corneum (SC) in two siblings with NS, and examined the involvement of these factors in the development of AD.

A 29-year-old Japanese man (patient 1) and his younger sister, a 24-year-old woman (patient 2), presented with erythroderma and ichthyosis linearis circumflexa (Fig. 1) over their entire bodies, as well as trichorrhexis invaginata. The height of patient 1 was 163 cm and weight 58 kg. His total serum IgE level was 1503 U mL⁻¹ (normal 12–310) and serum IL-18 level 564 pg mL⁻¹. Patient 2 had short stature (height 138 cm, weight 45 kg) and glaucoma. Her total serum IgE level was markedly elevated (47 200 U mL⁻¹), and serum IL-18 level was also increased (459 pg mL⁻¹). Serum IgE and IL-18 levels were measured by UniCAP[®] total IgE assay (Phadia AB, Uppsala, Sweden) and enzyme immunoassay (BML Inc., Tokyo, Japan), respectively. Their parents were second-degree cousins and were not affected by NS.



Fig 1. Erythematous patches bordered by polycyclic scaling with surrounding lichenified skin, compatible with ichthyosis linearis circumflexa on the lower leg of patient 2.

Mutation of SPINK5 in the two inbred NS siblings was examined by a polymerase chain reaction–direct sequencing technique as described previously.⁵ In both patients, a homozygous R790X nonsense mutation was found in exon 25 of SPINK5 (Fig. 2a). Both subjects gave written informed consent for this analysis, and this study was approved by the Ethics Committee of the Osaka City University Graduate School of Medicine. The caspase-1 activity of SC was examined using the synthetic peptide Ac-Tyr-Val-Ala-Asp-MCA (Peptide Institute, Osaka, Japan) as substrate. SC samples were obtained from the forearm of the two patients with NS and nine normal healthy controls using adhesive tape. Reaction mixtures with 100 µL of 1 mmol L⁻¹ substrates and 1 mg of SC (dry weight) were incubated at 37 °C for 2 h, as described previously.⁵ Measurements were made with an F-4500 fluorescence spectrophotometer (Hitachi Ltd, Hitachinaka, Japan) at excitation/emission 380/460 nm. Each assay was performed in duplicate.

Our two patients with NS exhibited markedly elevated serum IL-18 levels (564 and 459 pg mL⁻¹). Patients with conventional AD have been shown to have elevated serum IL-18 levels (mean 207 pg mL⁻¹) compared with controls (mean 144 pg mL⁻¹).⁶ It has been demonstrated that elevated IL-18 leads to Th2 cell development and induces features of AD,³ and that IL-18 is produced as pro-IL-18 and is activated by

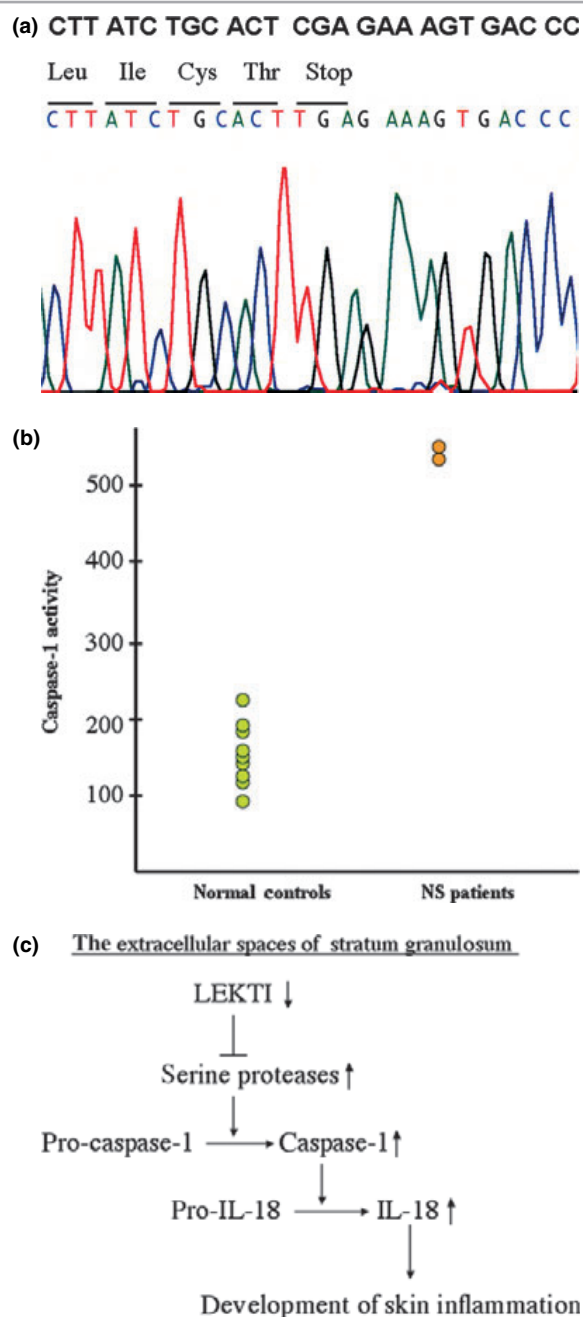


Fig 2. (a) Homozygous R790X nonsense mutation in SPINK5 of the patients with Netherton syndrome (NS) was detected using polymerase chain reaction–direct sequencing analysis. (b) Caspase-1 activity in stratum corneum (SC) of two patients with NS and nine healthy controls. Caspase-1 activity in SC was measured using the synthetic peptide Ac-Tyr-Val-Ala-Asp-MCA as substrate. The mean caspase-1 activity of SC in the patients with NS (524·95, range 522·9–527·0) was 3·3-fold that in the healthy controls (157·63, range 92·7–237·5). (c) Proposed pathophysiological cascade from LEKTI deficiency to development of skin inflammation. IL, interleukin.

caspase-1.⁴ We hypothesized that the high serum IL-18 levels in our two patients with NS are due at least in part to dysregulation of epidermal caspase-1 activity in NS.

We performed analyses of caspase-1 activity of SC in our patients with NS. The mean caspase-1 activities of SC in the patients with NS ($n = 2$) and in healthy controls ($n = 9$) were 524.95 (range 522.9–527.0) and 157.63 (range 92.7–237.5), respectively. The caspase-1 activity of SC in the patients with NS was 3.3-fold that in the healthy controls (Fig. 2b). Caspase-1 is synthesized as a procaspase-1, which is activated by proteolytic cleavage. In macrophage cytoplasm, a serine protease, tripeptidyl peptidase II, promotes maturation of caspase-1.⁷ However, in culture of keratinocytes, procaspase-1 and pro-IL-18 were activated in extracellular medium but not cell lysates.⁸ LEKTI is a serine protease inhibitor that is secreted into the extracellular spaces of the stratum granulosum (SG).⁹ The serine proteases kallikrein (KLK) 5 and KLK 7 are located in SG and regulate desquamation of SC.⁹ Skin barrier morphogenesis is regulated by the balance between LEKTI and serine proteases in SG. It is thus tempting to speculate that LEKTI inhibits caspase-1 activation in the extracellular spaces of SG through inhibition of serine proteases, and that reduction of LEKTI in the epidermis induces elevation of serum IL-18 levels in NS (Fig. 2c).

LEKTI deficiency may induce high caspase-1 activity in SC and may consequently increase IL-18 production. IL-18 upregulates interferon- γ production and Th2 cell development. The features of AD in NS may not be due to impairment of epidermal barrier function and may be exacerbated by activation of caspase-1 within the epidermis, leading to elevated serum levels of IL-18. LEKTI may play a significant role in attenuating skin inflammation, particularly in AD, by inhibition of caspase-1 activation within the epidermis. The LEKTI–serine protease–caspase-1–IL-18 cascade may thus prove useful as a target in novel treatments of NS and AD.

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A cautionary tale

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SIR, SIAscopy (SIA = spectrophotometric intracutaneous analysis) is a noninvasive method of scanning the skin using infrared radiation and visible light to yield information regarding the position of some of the cells and structures within the skin.

The incident light is read as it emerges back out of the skin; readings are fed into SIAscopy algorithms, and comparison is made with a proprietary mathematical model of the skin. The outputs of the algorithms are four images which depict the concentration of haemoglobin, melanin, collagen and dermal melanin within the area of skin that has been scanned.

Of interest is the quantity of collagen within the papillary dermis, vasculature of the skin, and distribution and quantity of melanin, especially relative to the dermoepidermal junction. Melanomas characteristically display a variety of features: (i) an erythematous blush at the invading margin of the superficial spreading lesion; (ii) displacement of blood in the papillary dermis by the invading regions; (iii) tumour punching holes in the papillary collagen; (iv) collagen arranged into rosettes and whorls around invasive nodules; and (v) dermal melanin in haphazard arrangements in invasive regions. Benign naevi, in contrast, display a regular arrangement of dermal and epidermal melanin, a homogeneous vascular pattern and homogeneous collagen arrangement.

Studies have shown that SIAscopy achieves a sensitivity of 93% and a specificity of 80% in the diagnosis of malignant melanoma if all five characteristics of melanoma are applied when scanning pigmented lesions,¹ hence demonstrating that